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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF SKIN DISORDERS

(57) Abstract

A process is provided which is suitable for the preparation of herbal compositions for the treatment of skin disorders such as eczema and psoriasis. The process comprises preparing an extract or extracts of herbs which provide an anti-inflammatory agent, an adrenocortical stimulant and a cortisol protecting agent by steam distillation and decoction and then treating the extracts to reduce the polysaccharide and/or sugar content. This is achieved by fermentation or enzymic action or by extraction with a solvent having a polarity in the range E° 0.4 to 0.95 or by precipitation with an inorganic compound and/or colloid or by a combination of two or more of the above. As a final concentration step the material is further purified by extraction with a solvent having a polarity in the range mentioned above. The reduction of the sugar/polysaccharide content greatly improves the handling characteristics of the extract which can be dried to a free flowing powder. Tablets and capsules for oral administration can be prepared from the extract and it is also suitable for the preparation of topical compositions.

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PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF SKIN DISORDERS

The present invention relates to extracts of herbal compositions for use in the treatment of skin disorders such as, for example eczema and psoriasis and to processes for their preparation.

The etiology of eczema and psoriasis is not completely understood. However the symptomotology which characterizes the conditions is well described. The most important features are:- inflammation and pruritus (itching) which leads to a cycle of further irritation, inflammation and itching.

Eczema and psoriasis are expressions of an inappropriate immunological response whereby the body reacts to some of its tissue components as though they were foreign. Treatment is directed towards diminishing the severity of the immune response and alleviating symptoms. In conventional Western medicine topical corticosteroids are used to reduce inflammation and to suppress the immune response. Emollients are used to physically protect and smooth the skin and, where the skin is infected, antiobiotics are used.

Practitioners in traditional Chinese medicine however use decoctions of herbs for oral and topical treatment of dermatological conditions including eczema and psoriasis. A wide variety of agents have been used and in traditional Chinese medicine it is conventional to use a compound prescription which is designed by the practitioner after careful examination of the individual patient. It has been found by clinical experimentation that mixtures of certain herbs can be used to provide a composition which is effective in a large proportion of patients suffering from eczema and psoriasis, without recourse

to individualisation of treatment. Different formulae have been devised for dry, weeping, infected and lichenified eczema although the mode of action of traditional Chinese medicines is not fully understood.

Table I shows a number of Chinese herbs which are traditionally used for the treatment of skin disorders together with the principle constituents and their pharmacological actions (Chang and But; Pharmacology and Applications of Chinese Materia Media. World Scientific Publishing 1986, Volumes I and II). The table shows that many of the agents traditionally used have pharmacological properties which are appropriate for the treatment of symptoms of eczema and psoriasis, namely anti-inflammatory, analgesic, anti-pyretic, anti-pruritic, anti-bacterial and immune suppressent activity. Some of the agents listed may stimulate the adrenal cortex to produce endogenous corticosteroids and others may inhibit the breakdown of cortisol in certain tissues such as the skin and lung. The combination of herbs to provide a combined attack on the symptoms of eczema and psoriasis are therefore rational even though at present it is not known exactly which of the constituents are responsible for the beneficial therapeutic effects of the mixtures.

It is possible that some of the herbs in the mixtures are necessary in order to increase the solubility of some of the active constituents in water since the traditional method of preparing extracts is by decoction i.e. boiling in water. In traditional Chinese medicine some herbs are included in prescriptions because they act as demulcents i.e. agents which have a soothing effect on the gastrointestinal tract and facilitate patient acceptance. It is firmly believed by traditional Chinese practitioners that the toxicity of mixtures

of herbs is less than that of the herbs given in isolation. Although this has yet to be rigorously proved in controlled clinical trials, conventional wisdom indicates that some of the herbal components have biological activities which summate, and others antagonise the toxic effect of active components. Until the active components have been identified with certainty it has proved prudent to use a decoction, extract or fractionated extract of a plurality of herbs. To be useful in practice it is necessary to have one or more fixed composition mixtures. Surprisingly, it has been found that fixed combinations of specific herbs can be used to treat different types of eczema and psoriasis.

For example a particularly useful formulation of 10 herbs which has been found to be effective in the treatment of dry ("red all over") childhood eczema can be prepared by adding about 300 ml of water to every 38.75g of herb contained in a (non-aluminium) saucepan, bringing to the boil and simmering for one and a half hours. During this process the volume of liquid is reduced until a volume of about 50 ml per 38.75g of original herb is obtained. The final volume of the decoction is not critical and when removed from the exhausted herbs can be diluted to taste. The decoction obtained from the herbs is prepared fresh each day. Some of the herbs contain volatile oil and these herbs are added three minutes before the end of the decoction period to minimise loss of volatile oil.

The process of decoction is efficient in the extraction of the active principals but additionally a large quantity of inactive material in the form of polysaccharides, colouring matter, sugars and tannins is also extracted. There is therefore a need for a method of preparing herbal extracts which are more

concentrated in respect of the active ingredients and contain much lower amounts of extraneous material than those extracts hitherto known.

The present inventors have devised a method by which this might be achieved which allows a smaller dosage unit to be administered.

Thus a process for the preparation of a composition for treating skin disorders in accordance with the invention comprises:-

(a) preparing an extract or extracts of a plurality of herbs, the herbs being such as to provide an anti-inflammatory agent, an adrenocortical stimulant and a cortisol-protecting agent by subjecting said herbs to steam distillation and decoction,

(b) reducing the amount of polysaccharides and/or sugars in at least a proportion of the extract or extracts to less than 5% by weight under conditions which do not substantially reduce the content of glycosides which are present in said material by one or more of:-

(i) fermentation or enzymatic action,

(ii) extraction with a solvent having a polarity in the range E^{o} 0.4 to 0.99 or a mixture of solvents at least one of which has a polarity in said range,

(iii) precipitation with an inorganic compound and/or a colloid,

and

(c) concentrating the active agents present in the extracted material by further extraction with a solvent having a polarity in the range E^{o} 0.4 to 0.99 or a mixture of solvents at least one of which has a polarity in said range.

The preparation of an extract in step (a) of the above method is advantageously carried out by the traditional decoction process of boiling the herbs in water. Prior to decoction any volatile oils or other volatile components can be removed from the herbs by steam distillation and retained for re-introduction into the final extract if desired. These volatile components can be particularly useful in the formulation of treatments for eczema and psoriasis.

The reduction of the polysaccharides and/or sugar carried out in step (b) is extremely important in the process of the invention. Extracts containing substantial amounts of sugars are very difficult to evaporate to a free flowing powder and often nothing more than a solid sticky mass can be achieved. Preferably the amount of polysaccharides and/or sugars is reduced to less than 2.5% and more preferably less than 5% by weight. It is also important that the step for reducing excess polysaccharides and sugars is carried out under conditions which do not substantially reduce the glycoside content since one or more of the active agents may be a glycoside.

Where the polysaccharide and/or sugar content is to be reduced by fermentation it is preferable to incubate the total water extraction from the

decoction prepared in step (a) with barley malt or with a yeast such as saccharomyces cerevisiae or a fungus such as Aspergillus oryzae or other microorganism providing amylase and/or saccharolytic enzymes. Isolated and purified amylolytic or saccharomytic enzymes may also be used, optionally bound to a membrane or other support. Where these enzymes will also split glycosides it is preferable to use an inhibitor of glycosidase.

In a fermentation process ethyl alcohol may be formed in situ and may be used in a further separation of active ingredients.

If the polysaccharide and/or sugar content is to be reduced by the further extraction of the initial extract with a solvent or mixture of solvents at least one of which has a polarity in the range E^{o} 0.4 to 99 it is preferable if the solvent is one or more of chloroform, methylene chloride, ethyl acetate, tetrahydrofuran, methylethylketone, acetone, acetonitrile, propanol, ethanol, methanol, industrial methylated spirits or a not less than 70% solution of one or more of the above in water. Particularly preferred are 70% solutions of ethanol, propanol or industrial methylated spirits.

The addition of these solvents results in a fractional precipitation of polysaccharide and/or sugars, the desired active components remaining in solution.

As an alternative to, or as well as fermentation, enzymic treatment and/or solvent extraction in step (b) the polysaccharide and/or sugar content can be reduced by precipitation with an inorganic compound and/or a colloid. A preferable inorganic compound for use is calcium hydroxide.

After the sugar reducing step a further concentration of the extract is generally required.

In particular it is desirable to substantially rid the extract of polyphenyls and tannins. In the process of the invention this is achieved by the further extraction step (c) using a solvent or mixture of solvents at least one of which has a polarity in the range E^{o} 0.4 to 0.95. Suitable solvents may be selected from the list given above in connection with step b(ii).

The extract produced by the process of the invention may be evaporated to a paste, mixed with excipients and extruded to granules for oral administration, optionally with the addition of flavourings.

The extract prepared may be diluted in an aqueous solution for oral administration. The invention particularly provides compositions containing the herbal extract made by the process of the invention containing an anti-inflammatory agent, an adrenocorticol stimulant and a cortisol protecting agent which is admixed with a pharmaceutically suitable excipient, diluent or carrier many examples of which are well known to the man skilled in the art. A particularly useful carrier is silica gel.

For example the composition may be prepared for topical administration using well established formulations which produce an emollient ointment or water dispensable cream. The composition may also be prepared in a unit dosage form such as a tablet or capsule for oral administration. For such use it is advantageous if after the final extraction step the herbal extract is processed to form a powder, for example by spray drying, freeze drying or evaporation.

Chinese medicine teaches that substantially all of the herbs in a composition are necessary for activity and that the herbs are best given in extemporaneously prepared decoction. However it has

now surprisingly been found that the anti-eczema activity of the composite herbal preparation resides mainly, if not exclusively in a restricted number of herbs. It is therefore possible to reduce the amount of unnecessary material from the composition by limiting the number of herbs used, and to then further reduce the quantity of material given by preparing a composition in concentrated form in accordance with the invention wherein extraneous materials are removed.

Herbs selected from the list in Table I are suitable for use in the invention and a particularly preferred composition is one containing extracts from Rehmannia glutinosa, Dictamnus augustifolia, Glycyrrhiza uralensis and either Ledebouriella sesloides or Schizonepeta tenuifolia. Optionally Tribulus terrestris can be included. Another preferred composition is one containing the first 10 herbs listed in Table I.

It is preferable if one of the herbs included in the mixture provides an anti-pruritic (anti-itching) agent. As some of the herbs may have a bitter taste it is also preferable to add a sweetening agent for oral compositions.

The herbal extract may be prepared in accordance with the invention either by carrying out steps (a), (b) and (c) on a plurality of herbs which are first mixed together or by carrying out steps (a), (b), (c) on some or all of the individual herbs and mixing together the final extracts.

A disadvantage of the former method is that the yield of active ingredient from each herb varies from batch to batch so that the final concentration of each active agent in the mixture will not be known. By preparing separate extracts of each herb and then later mixing them, each may be assayed using a marker

substance which assists in standardizing the dose given to the patient. A further advantage is that full processing for sugar reduction need only be carried out on those herbs in the mixture having a high polysaccharide or sugar/content which makes them difficult to handle.

The invention is now illustrated in the following non-limiting examples.

Example 1

The following ingredients are coarsely chopped or powdered and volatile oil is removed by steam distillation:

	Weight in Grams
Radix Ledebouriellae	112.5
Fructus Tribuli	112.5
Caulis Akebiae	112.5
Radix Rehmanniae (raw)	168.75
Radix Glycyrrhizae	56.25
Radix Paeonia rub.	112.5
Cortex Dictamni	168.75
Moutan radicis	112.5
Gypsum Fibrosum	450.0
Artemisia scopariae	112.5

The oil is reserved and the residue is mixed with one litre of water, boiled for one and a half hours and allowed to cool to a temperature of 35°C to form a decoction.

100 ml of an actively growing culture of fresh baker yeast is added to the mixture of herbs and water and maintained with stirring for 8 hours or until the sugar content of an aliquot is less than

0.4%.

The vegetable matter is removed by straining and yeast is removed from the liquor by centrifugation. The filtered liquid is evaporated to dryness.

The extract thus prepared is stirred with 200 ml of ethyl acetate for 10 minutes, separated by centrifugation and the solution reserved. A further quantity of 50 ml ethyl acetate is added, the mixture, stirred and separated. The combined filtrate is evaporated to dryness.

The reserved oil is added back. The resulting product is a brown extract which is free flowing and can be used, with suitable flavourings, as the dosage form. It can be formulated into conventional pharmaceutical dosage forms, with addition of excipients, for the treatment of dry eczema. The quality given above is sufficient for 10 days treatment of an adult.

Example 2

The following herbs are coarsely chopped or powdered and decocted with 4 litres of water for 1 hour:

	Weight in Grams
Radix Rehmanniae (raw)	168.75
Radix Paeonia rubra	112.50
Radix Glycyrrhizae	56.25
Cortex Dictamni radicis	168.75
Rhizoma Smilacis glabrae	168.75
Fructus Kochiae	56.25
Radix Angelica sinensis	112.50
Semen Sesami (black)	168.75

The liquor is removed by centrifugation. The extract is then evaporated until it contains 50% solids w/v and 10% by weight calcium hydroxide is added. Three volumes of isopropanol are added with mixing and the mixture allowed to stand at room temperature. The clear supernatant is removed, 1 volume of 75% isopropanol added, mixed and the residue centrifuged. The pooled supernatants are evaporated to dryness. The resulting refined extract can be mixed with pharmaceutical aids and filled into capsules or compressed into tablets.

Example 3

An extract containing the following herbs is prepared:

	Weight in Grams
Ledebouriella sesloides	10
Paeonia rubra	12
Rehmannia glutinosa	10
Glycyrrhiza uralenis	15

For the herbs Ledebouriella sesloides and Paeoniae rubra a decoction is prepared of each of the herbs individually by boiling in successive quantities of water until complete exhaustion of the marc. The extracts are dried.

Extracts of each of the herbs Rehmannia glutinosa and Glycyrrhiza uralenis are prepared by the method of Example 2. The dried extracts of all four herbs are combined in the weights shown above which provides an adult daily dose for the treatment of eczema.

Example 4

An extract is prepared from a mixture of the following herbs using the method described in Example 2:

	Weight in Grams
Radix Rehmanniae (raw)	90
Rhizoma Smilacis glabrae	90
Radix Glycyrrhizae	30
Cortex Dictamni Radicis	90
Radix Paeonia Rub	60
Radix Artemisia scopariae	60
Fructus Kochiae	30
Sophora flavescens	20
Rhizoma atractyloides	60

The composition is suitable for treatment of chronic, lichenified, "weeping" eczema, and the quanities given are suitable for 10 days treatment of an adult patient.

Example 5

An extract is prepared from a mixture of the following herbs using the method described in Example 2:

	Weight in Grams
Rhizoma Similacis glabrae	300
Cortex Dictamni Radicis	100
Radix Clematidis	100
Radix Angelica sinensis	100
Radix Polygonum multiflori	100
Radix Salvia miltiorrhiza	100
Rhizoma Ligustiae chuanxiong	100

The composition is suitable for treatment of "stable" psoriasis and the quanitites given are suitable for 10 days treatment of an adult patient.

Example 6

An extract is prepared from a mixture of the following herbs using the method described in Example 2:

	Weight in Grams
Rhizoma Smilacis glabrae	300
Cortex Dictamni Radicis	100
Radix Clematidis	100
Radix Rhemanniae	200
Rhizoma Imperata cylindrica	100
Radix Arnebiae (Ser) lithospermum	10
Radix Salvia miltiorrhiza	10
Radix Ligustiae chuanxiong	10
Carthamus tinctorus	10

The composition is suitable for the treatment of progressive psoriasis and the quantities given

above are suitable for 10 days treatment of an adult patient.

Example 7

A refined extract is prepared according to the method given in Example 2 from the following herbs and then mixed with an emulsifying ointment base to produce an oil/water cream:

Phellodendron anurense (extract from 20g herb)
Scutellaria baicalensis (extract from 20g herb)
Coptis chinensis (extract from 20g herb)
Cetomacrogol Emulsifying Ointment to 100g

Example 8

A refined extract is prepared according to the method given in Example 2 from Sophora flavescens, and incorporated in an emulsifying ointment base according to the following formula:

Sophora flavescens (extract from 20g herb)	
Emulsifying wax	30g
Hard paraffin	5g
Cod liver oil	15g
Evening Primrose Oil	15g
White Soft Paraffin to 100g	

This ointment can be applied thinly to the skin or can be mixed with water to produce an oil in water emollient cream.

Example 9

A refined extract prepared according to the

method given in Example 2 from Rheum palmatum is incorporated in an emulsifying ointment base:

Rheum Palmatum (extract from 30g herb)
Cetomacrogol Emulsifying Ointment to 100g

In this example and in Examples 7 and 8 the quantity of extract of herb is illustrative and not limited to the proportions given.

Example 10

A decoction was prepared using the method given in Example 1 from 38.75g of the herbs listed in that Example to give a final volume of 50ml. Using a proprietary test kit, approximate dilutions of the decoction were tested for sugar before, and at intervals after adding 3ml of a fresh 10% yeast suspension to the decoction. The mixture was incubated at 30°C with occasional stirring.

Time (h)	Approx concentration of sugar as tested	Dilution	Concentration in decoction by weight
0	>0.2%	1:300	>30%
½	0.2-0.4%	1:50	10-20%
1	0.2-0.4%	1:10	2-4
2	0.2-0.4%	1:1	0.2-0.4%

*Limit of detection of glucose oxidase test kit.

After fermentation, the decoction is markedly less sweet although there is residual sweetness contributed by the liquorice contained in the mixture. When the resulting solution is filtered and

evaporated to dryness 4.7g of extract is produced.

Example 11

The following herbs are coarsely chopped and volatile oil is removed by steam distillation:

	Weight in Grams
Radix ledebouriellae	300
Fructus Tribuli	300
Lacca	450
Caulis Akebiae	300
Radix glycyrrhizae	150
Radix Rehmanniae (raw)	450
Radix Paeonia rubra	300
Herba Lophatheri	300
Cortex Dictamni radicis	450
Herba Schizonepetae	150
	3100g

The oil is reserved and the residue is mixed with one litre of water, boiled for one and a half hours and allowed to cool to a temperature of 35°C to form a decoction.

100 ml of an actively growing culture of fresh bakers yeast is added to the mixture of herbs and water and maintained with stirring for 8 hours or until the sugar content of an aliquot is less than 0.4%.

The vegetable matter is removed by straining and yeast is removed from the liquor by centrifugation. The filtered liquid is evaporated to dryness.

The extract thus prepared is stirred with 200 ml of 70% industrial methylated spirits for 10

minutes, separated by centrifugation and the solution reserved. A further quantity of 50 ml 70% industrial methylated spirits is added, the mixture stirred and separated. The combined filtrate is evaporated to a syrupy consistancy. Weight per ml is determined and 1/3 of this weight of colloidal silica added, and the extract evaporated to dryness.

The resulting dry extract is a brown extract which is free flowing and can be used, with suitable flavourings, as the dosage form as powder, granules, capsules or tablets, for the treatment of dry eczema. These quantities are sufficient for 20 days treatment for an adult.

TABLE 1

CHINESE PLANT NAME	LATIN NAME	CONSTITUENTS	PHARMACOLOGY	TRADITIONAL USE IN CHINA
Bai Tai Weng	Potentilla chinensis	triterpenoid saponins	Antibacterial, anti-trichomonal, anti-amoebic	Bacillary dysentery, amoebic dysentery, lymph node TB, Squamous cell cancer
Dihuang	Rehmannia glutinosa (Libosch) (Scrophulariaceae)	ß-sitosterol, mannitol, stigmasterol, campesterol, catalpol, rehmannin, vitamin A	Reduction of cortisol, diuretic, anti-inflammatory, anti-fungal	Immunological diseases, infectious hepatitis, hypertension, neurodermatitis
Chi Shao	Radix paeoniae lactiflorae/veitchii (Ranunculaceae)	paeoniflorin, albiflorin, oxypaeoniflorin, benzoylpaeoniflorin, benzoic acid, tannin	Vasodilator. Increases coronary blood flow, increases myocardial oxygen, inhibits platelet aggregation, sedative, analgesic, antispasmodic, anti-inflammatory	Pain in chest, pain in abdomen, dysmenorrhoea, amenorrhoea, carbuncle, epistaxis, conjunctival congestion, traumatic injury
Bai Xan Pi	Dictamnus augustifolia Chinese Dittany Root bark + (Rutaceae)	Dictamnine, dictamnolactone, sitosterol, obacunic acid, trigonelline, choline campesterol, fraxinellone shimmianine fagarine, dasycarpamine	Cardiotonic, antifungal, smooth muscle stimulant, antipyretic, shortened clotting time (iv)	Anti-rheumatic, anti-inflammatory, pityriasis rosea, scabies, dermatomycoses, prurigo, rheumatic pain, jaundice

CHINESE PLANT NAME	LATIN NAME	CONSTITUENTS	PHARMACOLOGY	TRADITIONAL USE IN CHINA
Gan Cao	Glycyrrhiza uralensis (Fisch) Licorice (Leguminosae)	Triterpenes (glycyrrhizin 'G' etc) Flavonoids (liquiritin etc) Berniarin, umbelliferone, ferulic acid, sinapic acid etc.	Adrenocorticomimetic, anti-inflammatory, anti-ulcer, antispasmodic, detoxicant	Addisons Disease, gastric & duodenal ulcer, pulmonary TB, infectious hepatitis, eye inflammatory disease, purpina
Fang Feng	Ledebouriella sesloides	Volatile oil, mannitol, bitter glycosides, phenolic glycosides, polysaccharides, organic acids	Anti-inflammatory, analgesic, antipyretic, anti-convulsant, antimicrobial	Rosacea, common cold, elimination of heavy metals, pruritus, urticaria
Ci Ji Li (Bai Ji Li)	Tribulus terrestris/Fructus tribuli	Diosgenin, ruscogenin, hecogenin, tribuloside, kaempferol, rutoside, astragalin, harmine	Hypotensive effect on smooth muscle, diuretic, cough suppressant	Headache, dizziness, red eye, itching, chest
Dan Zhu Ye	Lopatheri gracile	Arundoin, cylindrin, friedelin, taraxerol, ß-sitosterol	Antibacterial, diuretic, antipyretic	Febrile disease, stomatitis, swelling & pain in gingivae, urethral inflammation and pain
Jing Jie Sui	Schizonepeta tenuifolia	d-menthone, l-pulegone, schizoneptosides A&B d-limone	Antipyretic, antibacterial, anti-inflammatory, analgesic, antitubercular	Influenza fever, headache, sore throat, measles, urticaria

CHINESE PLANT NAME	LATIN NAME	CONSTITUENTS	PHARMACOLOGY	TRADITIONAL USE IN CHINA
Mu Tong	Akebia trifoliata	Akebin which hydrolyses to hederagenin, oleandic acid, rhamnose & glucose	Diuretic, cardiotonic, stimulation of GI tract smooth muscle, uterine SM relaxant, antifungal	Urinary infections, oedemia, amenorrhoea, diarrhoea, period pain, prolapse uterus
Lei Gong Teng	Trypterigium wilfordii	Wilfordine, and related alkaloids, celacemine and other macrocyclic alkaloids, triptolide and other epoxyditerpenes, celastol and other triterpenes	Anti-inflammatory, antineoplastic, immunosuppressant, insecticide	Anthelmintic, anti-inflammatory, anti-rheumatic
Ku Shen	Sophora flavescens	Matrine, oxymatrine, sophoranol, flavonoids, cytosine	Diuretic, antineoplastic, immunosuppressant, bradycardia, reduced myocardial contractility, hypotensive, bronchodilator, anti-microbial	Anthelmintic, anti-inflammatory, jaundice, scabies, enteritis, dysentery
Bei Yin Chen	Artemesia scopariae	Volatile oil, cholorogenic acid, caffeic acid, capillarisin, methylcapillarisin, phenoxychromones, flavonoids	Antipyretic, cholagogue, hepatoprotective, antilipidaemic, hypotensive, antibacterial	Jaundice, hepatitis

CHINESE PLANT NAME	LATIN NAME	CONSTITUENTS	PHARMACOLOGY	TRADITIONAL USE IN CHINA
Mu Dan Pi (Moutan)	Paeonia suffructicosa	Paeonol, paeonoside, paeonolide, paeoniflorin, volatile oil, phytosterol	Antimicrobial, anti-inflammatory, hypotensive analgesic	Convulsions, ulcers, fractures, concussion, sprains
Zhi Mu	Anemarrhena asphodeloids	Saponins, sarsasapogenin, markogenin, neogitogenin, chimonin, isomangiferin	Adrenocortical stimulation, hypoglycaemic, antibacterial	Dry cough, fever
Dang Gui	Angelica sinensis	Volatile oil, ligustilide, butylidenephthalide, butanedioic acid, angelicane, ß-sitosterol, vitamins B_{12}, A & E, nicotinic acid, folic acid, ferulic acid, succinic acid	Immunosuppressant, anti-inflammatory, uterine relaxant, hypotensive, anti-platelet aggregation, antilipidaemic	Dysmenorrhea, anaemic, amenorrhoea, headache, constipation, rheumatism
Zi Cao	Lithospermum erythrorhizon	Acetylshikonin, ß-dimethylactylalkannin skikonin	Antineoplastic, antipyretic	Fever, eczema
Di Fu Zi	Kochia scopariae	Kochiasides	Anti-inflammatory	Eczema, pruritus, rheumatism
Tu Fu Ling	Smilacis Glabrae	Sarsagogenin, triterpene, glycosides	Immunosuppressant, anti-inflammatory	Eczema, leukorrhea, lymphedema, muscle cramp

CHINESE PLANT NAME	LATIN NAME	CONSTITUENTS	PHARMACOLOGY	TRADITIONAL USE IN CHINA
Chuan Xiong	Rh. Ligusticum chuanxiong	Volatile oil, alkaloids, phenolic compounds, Lactones	ß-agonist, coronary dilator, peripheral dilator, vasodilators, inhibition of platelet aggregation	Analgesic, rheumatism, sores, ulcers, dysmenorrhoea
Dan Shen	Salvia miltiorrhiza	Tanshinones I, IIa, IIb, miltirone, isotanshinones, salviol etc.	Improvement of circulation	Angina, pectoris, amenorrhoea, dysmenorrhoea, fractures, sprains, insomnia
He Shou Wu	Polygonum multiform	Anthraquinone, glycosides & aglycones	ß-blocker, lipid-lowering, antibacterial	Tinnitus, weakness of lower back, constipation
Bai Mao Gen	Imperata cylindrica	Cyclindrin, arunoin, ferneol	Diuretic, coagulant	Urinary tract infection, oedema, jaundice
Hong Hua	Carthamus tinctorius	Dihydroflavone, glycosides	Cardiotonic	Amenorrhoea, dysmenorrhoea, fractures, concussion, sprains
Cang Zhu	Atractylodes chinensis	ß-eudesmol, hinesol, atractylodin	Antiseptic. Hypoglycaemic, diuretic, gastritis, antispasmodic	Rheumatism, oedema, diarrhoea, abdominal distention
Wei Ling Xian	Clematis chinensis	protoanemonin, anemonol, sterols, saponins	Antihistaminic, antibacterial, induction of labour, vasodilator	Rheumatism, arthritis, numbness of limbs, traumatic injury, psoriasis

CHINESE PLANT NAME	LATIN NAME	CONSTITUENTS	PHARMACOLOGY	TRADITIONAL USE IN CHINA
Huang Bo	Phellandendron amurense	berberine, phellandendrine, magnoflorine, palmatine, obakulactone, obakunone	Anti-microbial Hypotensive muscle relaxant	Decongestant
Huang Qin	Scutellaria baicalensis	ß-sitosterol, benzoic acid, baicalein, baicalin, wogonin, wogonoside	Anti-microbial, sedative, antipyretic, hypotensive, anti-inflammatory, diuretic, anti-cholinergic	Fever, cough, pneumonia, jaundice, hepatitis, dysentery, conjunctivitis, hypertension
Huang Lian	Coptis chinensis	berberine, coptisine, worenine and other alkaloids	Antimicrobial, anti-cholinergic, hypotensive, muscle relaxant	Nausea, vomiting, dysentery, enteritis, conjunctivitis, otitis media
Da Huang	Rheum palmatum	anthraquinones, glycosides, sennosides tannins	Cathartic action, antispasmodic, choleretic action	Indigestion, jaundice, amenorrhoea, burns and scalds

Glossary of Terms

The terms used define the identity of the plant or ingredient are given in the examples as Latin binomial names. The parts of the plant used are defined as follows:-

Caulis	- Stem
Cortex	- Bark
Cortex radicis	- Root Bark
Herba	- Aerial parts
Fructus	- Fruit
Radix	- Root
Rhizoma	- Rhizome
Semen	- Seed
Spika	- Flowering spike

CLAIMS:

1. A process for the preparation of a composition for treating skin disease which process comprises:

(a) preparing an extract or extracts of a plurality of herbs, the herbs being such as to provide an anti-inflammatory agent, an adrenocortical stimulant and a cortisol-protecting agent by subjecting said herbs to steam distillation and decoction,

(b) reducing the amount of polysaccharides and/or sugars in at least a proportion of the extract or extracts to less than 5% by weight under conditions which do not substantially reduce the content of glycosides which are present in said material by one or more of:-

(i) fermentation or enzymatic action,

(ii) extraction with a solvent having a polarity in the range E^{o} 0.4 to 0.99 or a mixture of solvents at least one of which has a polarity within said range,

(iii) precipitation with an inorganic compound and/or a colloid,

and

(c) concentrating the active agents present in the extracted material by further extraction with a solvent having a polarity in the range E^{o} 0.4 to 0.99 or a mixture of solvents at least one of which has a polarity within said range.

2. A process as claimed in claim 1 wherein the polysaccharide and/or sugar content is reduced in step b(i) by fermentation with barley malt or a yeast such as Saccharomyces cerevisiae or Aspergillus oryzae.

3. A process as claimed in claim 1 wherein the polysaccharide and/or sugar content is reduced in step b(i) using isolated amylolytic or saccharolytic enzymes optionally in the presence of an inhibitor of glycosidase.

4. A process as claimed in claim 3 wherein the enzymes are bound to a membrane or other support.

5. A process as claimed in any preceding claim wherein when the polysaccharide and/or sugar content is reduced by the solvent extraction of the active agents in the method of step b(ii) the solvent is one or more of chloroform, methylene chloride, ethyl acetate, tetrahydrofuran, methylethylketone, acetone, acetonitrile, propanol, ethanol, methanol, industrial methylated spirits or not less than 70% solution of one or more of the above with water.

6. A process as claimed in claim 5 wherein the said solvent is ethyl acetate or is a 70% solution of ethanol, propanol or industrial methylated spirits.

7. A process as claimed in any preceding claim wherein when the polysaccharide and/or sugar content is reduced by the precipitation method of step (c) the inorganic compound is calcium hydroxide.

8. A process as claimed in any preceding claim wherein in the solvent extraction method of step (c) the solvent is one or more of chloroform, methylene chloride, ethyl acetate, tetrahydrofuran, methylethylketone, acetone, acetonitrile, propanol, ethanol, methanol, industrial methylated spirits or a not less than 70% solution of one or more of the above with water.

9. A process as claimed in claim 8 wherein the said solvent is ethyl acetate or a 70% solution of ethanol, propanol or industrial methylated spirits.

10. A process as claimed in claim 8 or claim 9 wherein tannins and polyphenyls are removed from the extracted material.

11. A process as claimed in any preceding claim wherein the volatile oils and other volatile components which are removed during steam distillation are retained and re-introducted into the composition.

12. A process as claimed in any preceding claim wherein the resulting herbal extract is processed to form a powder, for example by evaporation, spray drying or freeze drying.

13. A process as claimed in any one of claims 1 to 12 wherein the resulting herbal extract is dried to a paste, mixed with excipients and extruded to

form granules.

14. A process as claimed in any preceding claim wherein the herbs used in the preparation of the extract or extracts of step (a) of claim 1 are selected from the herbs set forth in Table 1.

15. A process as claimed in claim 14 wherein the extract or extracts contains constituents from the following herbs:-

(a) Rehmannia glutinosa to provide cortisol-protecting agent and adrenocortical stimulant,

(b) Dictamnus augustifolia to provide an alkaloid component,

(c) Glycyrrhiza uralensis to provide an adrenocortical stimulant, and

(d) either Ledebouriella sesloides or Schizonepeta tenuifolia to provide an anti-inflammatory agent.

16. A process as claimed in claim 15 wherein there is also used:-

(e) Tribulus terrestris.

17. A process as claimed in claim 14 wherein the herbs used to form the extract are the first 10 herbs of Table 1.

18. A herbal extract comprising an anti-inflammatory agent, an adrenocortical stimulant

and a cortisol-protecting agent when produced by a process as claimed in any one of the preceding claims.

19. A composition for the treatment of skin disease comprising the extract claimed in claim 18.

20. A composition as claimed in claim 19 when admixed with a pharmaceutical excipient, diluent or carrier.

21. A composition as claimed in claim 20 wherein the carrier is silica gel.

22. A composition as claimed in claim 19 or 20 which is prepared in unit dosage form.

23. A composition as claimed in claim 19 which is in the form of an aqueous solution.

24. A composition as claimed in claim 19 or 20 which is in the form of an ointment or cream.

25. The use of a herbal extract as claimed in claim 18 in the manufacture of a medicament for oral or topical treatment of skin disease.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00359

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K35/78; A61K7/48

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	WO,A,8 706 833 (CHEMEX PHARMACEUTICALS, INC.) 19 November 1987 see page 2, line 36 - page 3, line 11 see page 8, line 32 - line 33	1-25
A	GB,A,613 562 (JOSEPH HELLER) 30 November 1948	

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26 MAY 1992	11. 06. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	REMPP G.L.E.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200359 SA 57049

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 26/05/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU-A- 6729887	01-12-87
GB-A-613562		None	